Imaging Hyperpolarized ^{129}Xe Uptake in Pulmonary Barrier and Red Blood Cells Using a 3D Radial 1-Point Dixon Approach: Results in Healthy Volunteers and Subjects with Pulmonary Fibrosis

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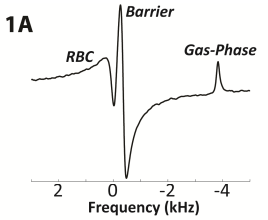
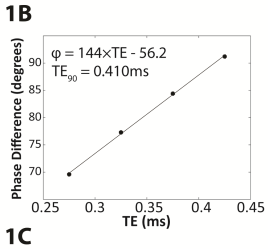
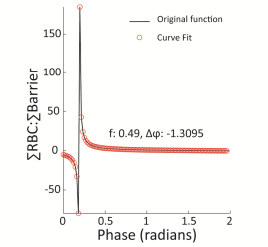
Target Audience: Hyperpolarized ^{129}Xe MRI, Clinical Functional Lung Imaging

Purpose: Current interest in hyperpolarized ^{129}Xe MRI has focused on exploiting its "dissolved-phase" resonances to probe pulmonary gas-exchange. It is now possible to image the dissolved-phase and gas-phase in a single breath-hold[1,2]. However, to obtain a truly fundamental insight into regional gas exchange the dissolved phase image must be separated into its two resonances - barrier tissue and plasma (197 ppm) and the RBCs (217 ppm). Such separation is particularly valuable in the study of pulmonary fibrosis (PF) patients, where we demonstrated that their pathologically thickened barrier tissue causes a ^{129}Xe transfer reduction to the RBCs pool by a factor of 3. We now seek to directly visualize and localize this signature of ^{129}Xe diffusion limitation by imaging the two dissolved-phase resonances separately. Recently, such separation was demonstrated in human subjects by Qing *et al.* using the hierarchical IDEAL algorithm[3]. While exceedingly elegant, this approach requires 3 progressively longer echo times that may be undermined by the short (~2ms[4]) T2* of dissolved-phase ^{129}Xe. We therefore, consider an alternative approach using a 1-pt Dixon method to image the dissolved phase ^{129}Xe at a single TE when the two resonances are 90° out of phase. This approach requires only a single sub-millisecond TE, and has been successfully demonstrated in small animals using both 2D and 3D acquisitions[5,6]. Here, we present the preliminary results of the clinical translation of this technique and its application to patients with PF.

Methods: Simultaneous gas and dissolved-phase images were acquired in 1 healthy volunteer and 5 subjects with IPF. Subjects inhaled 1-L of enriched ^{129}Xe polarized to 9±3%, and held their breath for 16-sec and were scanned as previously described[2] [matrix = 32×32×32, number of frames = 2002, TR=7.5ms, FOV=40cm, BW=15.63kHz, flip-angle (Dissolved/Gas) = 22°/0.5°]. The TE was set to ensure that the RBC and barrier resonances were 90° out of phase (TE_{90}). This was determined by taking dissolved phase spectra at 4 different echo times (TE = [0.275,0.325,0.375,and 0.425ms], TR=250ms, points=512, NEX=50, flip-angle=22°).The first 25 spectra at each TE were discarded to negate the effects of ^{129}Xe magnetization outside the gas exchange tissues, and the final 25 were averaged and fit to extract the phase difference between the dissolved-phase resonances. This RBC-barrier phase difference versus TE was fit by linear regression to determine TE_{90} (**Figure 1B).** The dissolved- and gas-phase images were reconstructed using a NUFFT algorithm and a phase shift $\Delta\phi$ was applied such that the RBC signal was in phase with the receiver. The required shift was empirically determined by requiring the RBC-barrier ratio obtained from imaging to equal the ratio from spectroscopy[3]. This was done by multiplying the image by a full range of phase angles from $-\pi$ to π, summing up the RBC and barrier pixels, taking their ratio, and fitting it to the function $\frac{RBC}{Barrier} = \frac{f\cos(\varphi_0+\Delta\varphi)-\sin(\varphi_0+\Delta\varphi)}{f\sin(\varphi_0+\Delta\varphi)+\cos(\varphi_0+\Delta\varphi)}$, where f is the spectroscopic RBC/barrier ratio, ϕ_0 is the true phase offset between the RBC signal and receiver and $\Delta\phi$ is the applied phase offset. The resulting RBC and barrier images were then corrected for B_0 inhomogeneity by using a phase map obtained from the single-resonance gas-phase ^{129}Xe image[3].







Results: Simultaneous gas and dissolved-phase images were successfully acquired in all subjects. **Figure 1A** shows the dissolved-phase spectrum at TE_{90} obtained in the healthy volunteer. The RBC-Barrier ratio for this subject was 0.48 and multi-echo spectroscopy yielded a TE_{90} of 0.41ms (**Figure 1B**). This $TE_{90,}$ although generally between 0.2 and 0.41ms varied somewhat among subjects as did the frequency of the RBC resonance. The receiver phase offset shown in **figure 1C** was used to rephase the dissolved-phase data, such that the real channel contained the RBC signal and the imaginary, the barrier signal. **Figure 2** shows one axial slice from each of the 3D isotropic images of gas-phase, barrier and RBC for the healthy volunteer and a subject with PF. The RBC distribution in the healthy subject was generally more homogenous and favored the gravitationally dependent lung. By contrast, the PF subject showed heterogeneous regions of RBC enhancement as well as patches of low uptake, which likely reflect regions of diffusion impairment.

Discussion and Conclusion: These preliminary results show the feasibility of a 1-point Dixon-based 3D radial sequence to simultaneously image all three resonances of ^{129}Xe in the lung. This should enable us to quantify regions of diffusion limitation, and generate useful regional biomarkers of pulmonary structure and function.

References: **1**. Mugler *et al.*, PNAS 2010. **2**. Kaushik *et al.*, JAP 2013. **3**. Qing *et al.*, JMRI 2013. **4**. Mugler *et al.*, ISMRM 2012. **5**. Driehuys *et al.*, PNAS 2006. **6**. Cleveland *et al.*, ISMRM 2013.

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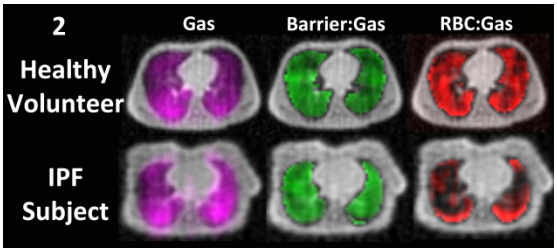

Figure 1: **(A)** Dissolved-phase spectrum from a healthy volunteer with the RBC and barrier resonances 90° out of phase. **(B)** The phase difference between the RBC and barrier resonances as a function of TE. **(C)** The RB ratio from imaging as a function of phase used to calculate the receiver phase-offset ($\Delta\phi$). **Figure 2**: Shows images of ^{129}Xe in the different compartments of the lung. The barrier and RBC images are normalized by the corresponding gas-phase images and expressed as ratios. While the barrier image is relatively homogenous in both the healthy volunteer and diseased lung, the RBC:gas image in the PF subject is extremely heterogeneous.